Claims

1. A screening method for the identification of agents which modulate, either directly or indirectly, the interaction of a first polypeptide encoded by a nucleic acid molecule selected from the group consisting of:

a) a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence as represented in Figure 17a or 17b;

b) a polypeptide encoded by a nucleic acid molecule which hybridises to the nucleic acid molecule in (a) and which enhances the pro-apoptotic activity of p53;

c) a polypeptide encoded by a nucleic acid molecule consisting of a nucleic acid sequence that is degenerate as a result of the genetic code to a nucleic acid molecule as defined in (a) and (b); with a second polypeptide selected from the group consisting of:

d) a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence as represented in Figure 18a, 18c, 18e or 18g;

e) a polypeptide encoded by a nucleic acid molecule which hybridises to the nucleic acid molecule in (d) above and which has the activity associated with Ras or a variant Ras polypeptide;

f) a polypeptide encoded by a nucleic acid molecule consisting of a nucleic acid sequence that is degenerate as a result of the genetic code to a nucleic acid molecule as defined in (d) and (e); comprising,

i) forming a preparation comprising said first and second polypeptide;

ii) adding at least one candidate agent to be tested; and

iii) determining the effect, or not, of said agent on the interaction of said first polypeptide with said second polypeptide.

2. A method according to Claim 1 wherein said first polypeptide is represented by the amino acid sequence as shown in Figure 17c or 17d, or a variant polypeptide wherein said variant polypeptide sequence has been altered by addition, substitution or deletion of at least one amino acid residue.

3. A method according to Claim 1 or 2 wherein said first polypeptide comprises the amino acid sequence + 1 to +120 of the sequence shown in Fig 17c and 17d .

4. A method according to Claim 3 wherein said polypeptide consists of the amino acid sequence +1 to +120 of the sequence shown in Figure 17c or 17d.

5. A method according to any of Claims 1-4 wherein said second polypeptide is represented by the amino acid sequence shown in Figure 18b, 18d, 18f or 18h, or a variant polypeptide wherein said variant polypeptide sequence has been altered by addition, substitution or deletion of at least one amino acid residue.

6 A method according to Claim 5 wherein said second polypeptide comprises the amino acid sequence as shown in Figure 18d.

7. A method according to Claim 5 or 6 wherein said second polypeptide comprises the amino acid sequence as shown in Figure 18h.

8. A method according to any of Claims 1-4 wherein said second polypeptide is modified at amino acid residue 17.

9. A method according to Claim 8 wherein said modification is the substitution of a serine amino acid for an asparagine amino acid.

10. A method according to any of Claims 1-9 wherein said first and second polypeptides are expressed by a cell.

11. A method according to Claim 10 wherein said cell is a cell transfected with at least one nucleic acid molecule(s) which encodes said first and second polypeptides.

12. A method according to Claim 10 or 11 wherein the expression of said nucleic acid molecule(s) is regulatable.

13. A method according to any of Claims 10-12 wherein said cell is a cancer cell.

14. A method according to any of Claims 10-13 wherein said cell is part of a transgenic animal wherein the genome of said animal has been modified to include nucleic acid molecules which encode first and second polypeptides.

15. A method according to any of Claims 10-14 wherein said nucleic acid molecules are expressed in a specific cell/tissue.

16. A screening method for the identification of agents which modulate, either directly or indirectly, the phosphorylation of a first polypeptide encoded by a nucleic acid molecule selected from the group consisting of:

a) a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence as represented in Figure 17a or 17b;

b) a polypeptide encoded by a nucleic acid molecule which hybridises to the nucleic acid molecule in (a) and which enhances the pro-apoptotic activity of p53;

c) a polypeptide encoded by a nucleic acid molecule consisting of a nucleic acid sequence that is degenerate as a result of the genetic code to a nucleic acid molecule as defined in (a) and (b); with a second polypeptide selected from the group consisting of:

d) a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence as represented in Figure 19a or 20a;

e) a polypeptide encoded by a nucleic acid molecule which hybridises to the nucleic acid molecule in (d) above and which has protein kinase activity;

f) a polypeptide encoded by a nucleic acid molecule consisting of a nucleic acid sequence that is degenerate as a result of the genetic code to a nucleic acid molecule as defined in (d) and (e); comprising,

i) forming a preparation comprising said first and second polypeptide;

ii) adding at least one candidate agent to be tested; and

iii) determining the effect, or not, of said agent on the phosphorylation state of said first polypeptide.

17. A screening method for the identification of agents which modulate, either directly or indirectly, the phosphorylation state of a first polypeptide encoded by a nucleic acid molecule selected from the group consisting of:

a) a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence as represented in Figure 17a or 17b;

b) a polypeptide encoded by a nucleic acid molecule which hybridises to the nucleic acid molecule in (a) and which enhances the pro-apoptotic activity of p53;

c) a polypeptide encoded by a nucleic acid molecule consisting of a nucleic acid sequence that is degenerate as a result of the genetic code to a nucleic acid molecule as defined in (a) and (b); with a second polypeptide selected from the group consisting of:

d) a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence as represented in Figure 21a;

e) a polypeptide encoded by a nucleic acid molecule which hybridises to the nucleic acid molecule in (d) above and which has protein phosphatase activity;

f) a polypeptide encoded by a nucleic acid molecule consisting of a nucleic acid sequence that is degenerate as a result of the genetic code to a nucleic acid molecule as defined in (d) and (e); comprising,

i) forming a preparation comprising said first and second polypeptide;

ii) adding at least one candidate agent to be tested; and

iii) determining the effect, or not, of said agent on the phosphorylation state of said first polypeptide.

18. A method according to any of Claims 1-17 wherein said agent is a polypeptide.

19. A method according to Claim 18 wherein said polypeptide is an antibody, or active binding fragment thereof.

20. A method according to Claim 19 wherein said antibody or binding fragment is a monoclonal antibody.

21. A method according to Claim 19 or 20 wherein said antibody fragment is a single chain antibody variable region fragment or a domain antibody fragment.

22. A method according to Claim 19 or 20 wherein said antibody is a humanised or chimeric antibody.

23. A method according to any of Claims 1-17 wherein said agent is a peptide.

24. A method according to any of Claims 1-17 wherein said agent is an aptamer.

25. A cell transfected with at least one nucleic acid molecule wherein the genome of said cell is modified to include at least one copy of a nucleic acid molecule encoding a polypeptide selected from the group consisting of:

a) a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence as represented in Figure 17a or 17b;

b) a polypeptide encoded by a nucleic acid molecule which hybridises to the nucleic acid molecule in (a) and which enhances the pro-apoptotic activity of p53;

c) a polypeptide encoded by a nucleic acid molecule consisting of a nucleic acid sequence that is degenerate as a result of the genetic code to a nucleic acid molecule as defined in (a) and (b); and at least one copy of a nucleic acid molecule encoding a polypeptide selected from the group consisting of:

d) a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence as represented in Figure 18a, 18c, 18e or 18g;

e) a polypeptide encoded by a nucleic acid molecule which hybridises to the

nucleic acid molecule in (d) above and which has the activity associated with Ras or a variant Ras polypeptide;

f) a polypeptide encoded by a nucleic acid molecule consisting of a nucleic acid sequence that is degenerate as a result of the genetic code to a nucleic acid molecule as defined in (d) and (e) wherein said cell is adapted for the regulated expression of said nucleic acid molecule(s).

26. A cell transfected with at least one nucleic acid molecule wherein the genome of said cell is modified to include at least one copy of a nucleic acid molecule encoding a polypeptide selected from the group consisting of:

a) a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence as represented in Figure 17a or 17b;

b) a polypeptide encoded by a nucleic acid molecule which hybridises to the nucleic acid molecule in (a) and which enhances the pro-apoptotic activity of p53;

c) a polypeptide encoded by a nucleic acid molecule consisting of a nucleic acid sequence that is degenerate as a result of the genetic code to a nucleic acid molecule as defined in (a) and (b) and at least one copy of a nucleic acid molecule encoding a polypeptide selected from the group consisting of;

d) a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence as represented in Figure 19a or 20a;

e) a polypeptide encoded by a nucleic acid molecule which hybridises to the nucleic acid molecule in (d) above and which has protein kinase activity;

f) a polypeptide encoded by a nucleic acid molecule consisting of a nucleic acid sequence that is degenerate as a result of the genetic code to a nucleic acid molecule as defined in (d) and (e) wherein said cell is adapted for the regulated expression of said nucleic acid molecule(s).

27. A cell transfected with at least one nucleic acid molecule wherein the genome of said cell is modified to include at least one copy of a nucleic acid molecule encoding a polypeptide selected from the group consisting of:

a) a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid

sequence as represented in Figure 17a or 17b;

b) a polypeptide encoded by a nucleic acid molecule which hybridises to the nucleic acid molecule in (a) and which enhances the pro-apoptotic activity of p53;

c) a polypeptide encoded by a nucleic acid molecule consisting of a nucleic acid sequence that is degenerate as a result of the genetic code to a nucleic acid molecule as defined in (a) and (b) and at least one copy of a nucleic acid molecule encoding a polypeptide selected from the group consisting of;

d) a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence as represented in Figure 21a;

e) a polypeptide encoded by a nucleic acid molecule which hybridises to the nucleic acid molecule in (d) above and which has protein phosphatase activity;

f) a polypeptide encoded by a nucleic acid molecule consisting of a nucleic acid sequence that is degenerate as a result of the genetic code to a nucleic acid molecule as defined in (d) and (e) wherein said cell is adapted for the regulated expression of said nucleic acid molecule(s).

28. A cell according to any of Claims 25-27 wherein said cell further comprises a nucleic acid molecule which includes a reporter gene to monitor the activity of said pro-apoptotic polypeptide(s).

29. A cell according to any of Claims 25-28 wherein said cell is a cancer cell.

30. A non-human transgenic animal comprising at least one cell according to any of Claims 25-29.

31. An animal according to Claim 30 wherein said non-human animal is a non-human primate.

32. An animal according to Claim 30 wherein said transgenic animal is a rodent.

33. An animal according to Claim 30 wherein said transgenic animal is a pig.

34. A combined preparation of p53 and ASPP1 and/or ASPP2.

35. A combined preparation comprising a nucleic acid molecule which encodes a p53 polypeptide, or sequence variant thereof, and at least one nucleic acid molecule which encodes at least one polypeptide, or sequence variant thereof, as represented by the amino acid sequences shown in Figure 17c and/or Figure 17d.

36. A preparation according to Claim 35 wherein both a p53 polypeptide and at least one polypeptide as represented by the amino acid sequences shown in Figure 17c and/or Figure 17d is encoded by a single nucleic acid molecule.

37. A preparation according to Claim 35 or 36 wherein said nucleic acid molecule is part of a vector.

38. A preparation according to Claim 37 wherein said nucleic acid molecules are operably linked to at least one promoter sequence which controls expression of said nucleic acid molecules.

39. A method to treat a condition which would benefit from an increase in apoptosis comprising administering a preparation comprising a first nucleic acid molecule comprising a nucleic acid sequence which encodes a p53 polypeptide, or sequence variant thereof, and administering a second preparation comprising a second nucleic acid molecule comprising a nucleic acid sequence which encodes a polypeptide, or sequence variant thereof, as represented by the amino acid sequence as shown in Figure 17c and/or Figure 17d wherein said preparations are administered simultaneously, sequentially or delayed manner.

40. A method to treat a condition which would benefit from a stimulation of apoptosis comprising administering a combined preparation according to any of Claims 34-38.

41. A method according to Claim 39 or 40 wherein said condition is cancer.

42. An antibody, or active binding fragment thereof, wherein said antibody or fragment, specifically binds a polypeptide encoded by a nucleic acid molecule selected from the group consisting of:

a) a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence as represented in Figure 17a or 17b;

b) a polypeptide encoded by a nucleic acid molecule which hybridises to the nucleic acid molecule in (a) and which enhances the pro-apoptotic activity of p53;

c) a polypeptide encoded by a nucleic acid molecule consisting of a nucleic acid sequence that is degenerate as a result of the genetic code to a nucleic acid molecule as defined in (a) and (b), wherein said antibody binds a phosphorylated epitope.

43. An antibody according to Claim 42 wherein said antibody is a monoclonal antibody.

44. An antibody according to Claim 42 or 43 wherein said antibody fragment is a single chain antibody fragment or a domain antibody.

45. An antibody according to any of Claims 42-44 wherein said phosphorylated epitope comprises amino acid residue 671 of the amino acid sequence as shown in Figure 17c.

46. An antibody according to any of Claims 42-44 wherein said phosphorylated epitope comprises amino acid residue 698 of the amino acid sequence shown in Figure 17d.

47. An antibody according to any of Claims 42-44 wherein said phosphorylated epitope comprises amino acid residue 746 of the amino acid sequence as shown in Figure 17c.

48. An antibody according to any of Claims 42-44 wherein said phosphorylated epitope comprises amino acid residue 827 of the amino acid sequence shown in Figure 17d.